university of groningen

University Medical Center Groningen

University of Groningen

Highly efficient ytterbium triflate catalyzed Michael additions of alpha-nitroesters in water

Keller, E; Feringa, B.L.

Published in:
Synlett

DOI:
10.1055/s-1997-5761

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1997

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Keller, E., & Feringa, B. L. (1997). Highly efficient ytterbium triflate catalyzed Michael additions of alpha-nitroesters in water. *Synlett*, *1997*(7), 842-&. https://doi.org/10.1055/s-1997-5761

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 05-05-2023

Highly Efficient Ytterbium Triflate Catalyzed Michael Additions of α-Nitroesters in Water

Erik Keller and Ben L. Feringa*

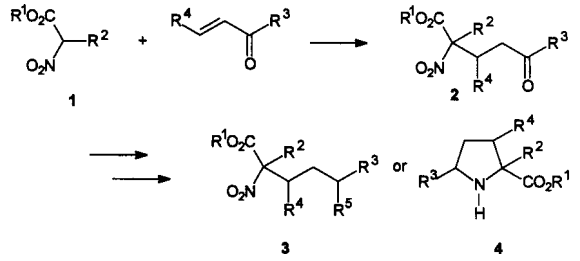
Department of Organic and Molecular Inorganic Chemistry, Groningen Centre for Catalysis and Synthesis, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

Feringa@chem.rug.nl

Received 29 April 1997

Abstract: Michael additions of α-nitroesters with enones and α,β-unsaturated aldehydes result in quantitative conversions to the corresponding 1,4-adducts by performing the reactions in water in the presence of ytterbium triflate as water-tolerant Lewis acid.

In recent years there has been growing recognition that water is an attractive medium for many organic reactions,[1] in particular when one considers the need to develop environmentally acceptable chemical processes.[2] Although it is by far the most common liquid in our environment, water as a solvent was not frequently used until recently for several reasons such as insolubility of the reactants or the reactivity of reagents towards water. This is especially true for Lewis acids such as $AlCl_3$, $TiCl_4$, or BF_3. Lanthanide triflates however have been described as effective water-tolerant Lewis acids in several carbon-carbon forming reactions such as Michael, aldol, and Diels-Alder reactions,[3] and in some cases the presence of water even improves their activity.[4] Nitroacetic acid derivatives **1** are valuable intermediates for the synthesis of many nitro and amino containing compounds.[5] Michael additions of **1** to enones opens a very attractive route towards functional (α-alkylated) amino acids **3** and substituted proline derivatives **4** *via* subsequent reductive cyclization of the nitro keto esters **2** obtained (Scheme 1).[6] However, Michael reactions of α-nitro esters under basic conditions often suffer from low yields.[5]

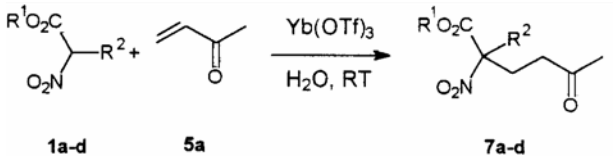


Scheme 1

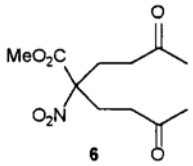
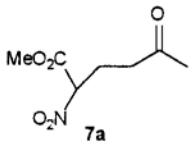
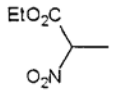
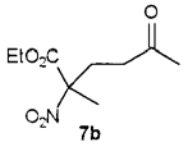
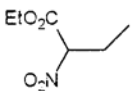
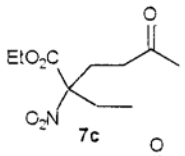
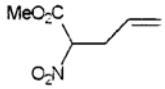
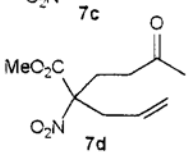
To our knowledge, only one example of a Lewis acid catalyzed Michael addition of α-nitroesters has appeared in the literature.[7] Rather drastic conditions were however required in this reaction catalyzed by copper(II) acetate in refluxing dioxane and reaction times of six days were needed.

As part of our interest in catalytic carbon-carbon bond forming reactions by conjugate addition reactions,[8,9] we reported the catalytic Michael addition of β-ketoesters towards enones and α,β-unsaturated aldehydes in water, resulting in the corresponding Michael adducts in nearly quantitative yield.[10] These very promising results prompted us to investigate the use of lanthanide triflates as reusable Lewis acid catalysts in Michael reactions of α-nitroesters in water as the solvent. We now report a highly efficient catalytic Michael addition of α-nitroesters in water at room temperature in the presence of a catalytic amount of ytterbium triflate ($Yb(OTf)_3$) as Lewis acid.[11] When the 1,4-addition of methyl nitroacetate (**1a**)[12] to methyl vinyl ketone (**5a**,R^3=H, MVK) was performed in water in the presence of 10 mol% of $Yb(OTf)_3$, bis-Michael adduct **6** was isolated in a quantitative yield, when two equivalents of MVK were used. With one equivalent of MVK the mono-Michael adduct **7** was found exclusively (Table 1).

Table 1. Michael Addition of α-Nitroesters **1a-d** and Methyl Vinyl Ketone **5a**



1a-d **5a** **7a-d**

Entry	Michael donor[a]	Michael adduct	Yield (%)
1	 **1a**	 **6**	99
2	 **1a**	 **7a**	98
3	 **1b**	 **7b**	99
4	 **1c**	 **7c**	98
5	 **1d**	 **7d**	96

[a] Catalyst $Yb(OTf)_3$ solvent H_2O. Michael acceptor MVK

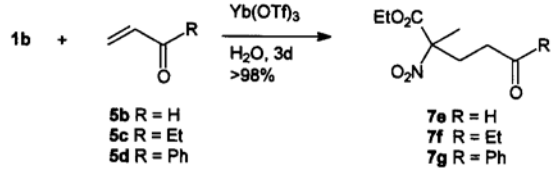
Also α-nitroesters bearing an alkylsubstituent at the α-position[13] give the corresponding Michael adducts in quantitative yield in the reaction with MVK in water as the solvent in the presence of 10 mol% of $Yb(OTf)_3$. In the absence of $Yb(OTf)_3$ the reaction is much slower, giving a low conversion to the desired Michael adduct even after prolonged reaction times. Unfortunately methyl-2-nitrophenylpropionate (**1e**) proved to be unreactive under the present conditions, giving only traces of the desired Michael adduct and mainly recovery of the starting material even after prolonged reaction times.

It should be emphasized that single products were obtained using this simple procedure and in most cases no further purification was

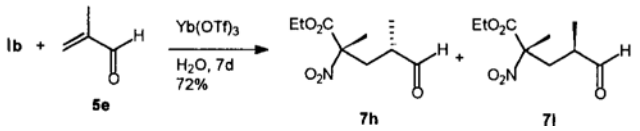
necessary, since the Michael addition was not accompanied by unwanted O-alkylation or hydrolysis of the ester functionality.

Furthermore α,β-unsaturated enones bearing various substituents at the α'-position **5b-d** were employed, again quantitative yields of the 1,4-adducts were found; typical examples are listed in Scheme 2. However when cyclic or β-substituted α,β-unsaturated enones were used no reaction was observed even after prolonged reaction times and only starting materials were recovered. With the Michael acceptors bearing various electron withdrawing groups only acrolein did give the desired 1,4-adduct, whereas α,β-unsaturated esters or nitriles are not reactive under these conditions. This trend in reactivity in water was also observed for the $Yb(OTf)_3$ catalyzed Michael addition of β-ketoesters.[10]

As an example of a Michael acceptor bearing a substituent at the α-position methacrolein was reacted with **1b**. Although the reaction afforded Michael adducts **7h** and **7i** as a mixture of diastereoisomers a reaction time of 170h was required to give nearly complete conversion of the starting materials, and the adduct could be isolated in only 72 % yield after flash chromatography since the 1,4-addition was accompanied by the polymerisation of the Michael acceptor.[14]

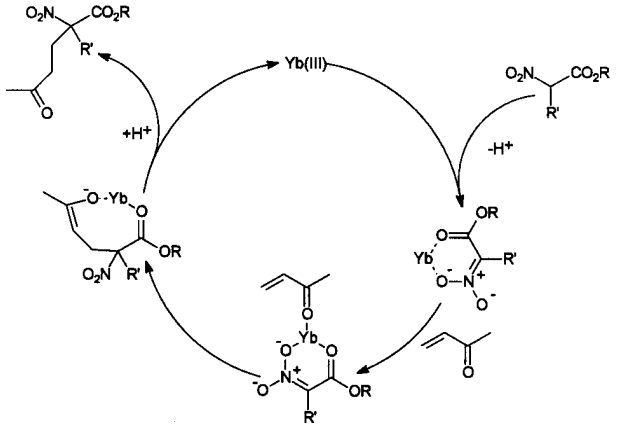


Scheme 2



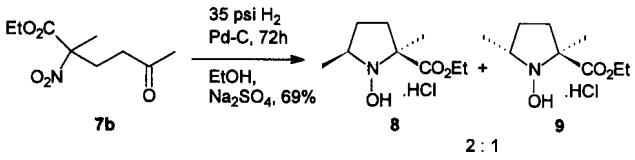
Scheme 3

The addition is proposed to proceed via a twofold coordination of the α-nitro ester by ytterbium triflate as well as by activation of the Michael acceptor as depicted in Scheme 4.



Scheme 4 (counterions omitted for clarity)

As an example to illustrate the synthetic versatility offered by this new catalytic Michael addition, the ethyl-2-nitro-2-methyl-5-oxo-hexanoate (**7b**) was hydrogenated in a Parr apparatus (35 psi H_2) using 10% palladium on coal and anhydrous sodium sulfate in ethanol.[15] After 72 hours the suspension was filtered over celite and the solvent was removed *in vacuo*. The residual oil was dissolved in diethyl ether and HCl was bubbled through the solution after which N-hydroxy-pyrrolidines **8** and **9** crystallized as the HCl-salt as a 2:1 mixture of *cis* and *trans* isomers.



Scheme 5

In summary, an efficient ytterbium triflate catalyzed Michael addition in water to both alkyl substituted and unsubstituted α-nitroesters was found. This new procedure provides an easy entry to functional amino acids or pyrrolidines.

Acknowledgement: This reseach was financially supported by the Netherlands Institute for Catalysis Research (NIOK), research project: catalysis in water.

References and Notes

1. For recent reviews see: Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023; Chan, T.H., Li, C.-J. *Can. J. Chem.* **1994**, *72*, 1181; Lubineau, A., Augé, J., Queneau, Y. *Synthesis* **1994**, 741.
2. Cornils, B., Wiebus, E. *Recl. Trav. Chim. Pays Bas* **1996**, *115*, 211.
3. For a review see: Engberts, J.B.N.F., Feringa, B.L., Keller, E., Otto, S. *Recl. Trav. Chim. Pays Bas* **1996**, *115*, 457.
4. Kobayashi, S. *Synlett* **1994**, 689.
5. Shipchandler, M.T. *Synthesis* **1979**, 666.
6. Osugi, K. *J. Pharm. Soc. Jpn.* **1957**, *77*, 630.
7. Coda, A.C., Desimoni, G., Invernizzi, A.G., Righetti, P.P., Seneci, P.F., Tacconi, G. *Gazz. Chim. Ital.* **1985**, *115*, 111.
8. Feringa, B.L., de Vries, A.H.M. in *Carbon-Carbon Bond Formation by Catalytic Enantioselective Conjugate Addition* Chapter in *Advances in Catalytic Processes* JAI Press Inc. **1995**, Vol. 1, 151.
9. Feringa, B.L., Jansen, J.F.G.A. In *Houben-Weyl*, 4th. Ed., Vol. E21, Chapter 1.5.2.4. Thieme, Stuttgart, 1995; p 2104; Jansen, J.F.G.A., Feringa, B.L. *J. Org. Chem.* **1990**, *55*, 4168; de Vries, A.H.M., Feringa, B.L. *Tetrahedron* **1994**, *50*, 4479; de Vries A.H.M., Feringa, B.L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.
10. Keller, E., Feringa, B.L. *Tetrahedron Lett.* **1996**, *37*, 1879.
11. In a typical procedure 1.0 mmol of α-nitroester was added to 10 ml of 0.01 M solution of ytterbium triflate. To this mixture were added 3 equiv. of α,β-unsaturated ketone and the mixture was stirred for 3 d at RT until complete conversion. The volatile components (excess enones) were evaporated under reduced pressure and the remaining aqueous solution was extracted three times with 10 mL of CH_2Cl_2. The solvent of the combined organic fractions was evaporated under reduced pressure and the residual colorless oil stripped with toluene to give the pure Michael adduct in nearly quantitative yield. When non-volatile enones were used, the Michael adducts could be isolated in nearly quantitative yield after column chromatography (SiO_2, ethyl acetate:hexane = 1:9). All spectroscopic and analytic data are in accordance with the proposed structures.
12. Zen, S., Koyama, M., Koto, S. *Org. Synth.* **1976**, *55*, 77.

13. Kornblum, N., Blackwood, R.K., Powers, J.W. *J. Am. Chem. Soc.* **1957**, *79*, 2507.

14. This side reaction was not observed for the other Michael acceptors used.

15. A mixture of 1.0 g (4.99 mmol) of ethyl-2-nitro-2-methyl-5-oxo-hexanoate (**7b**), 0.5 g Na_2SO_4 and 0.25 g 10% palladium on carbon in 25 mL anhydrous ethanol was shaken in a Parr apparatus for 72 h. After filtration over celite, the solvent was removed *in vacuo* and the residual oil was dissolved in 100 mL dry diethyl ether. HCl was bubbled through for 30 min. during which the hydroxyl pyrrolidine (mixture of *cis* and *trans* isomers) crystallized as the HCl-salt: (0.754 g white powder, 3.4 mmol, 69 %). **8** *Cis* isomer: ^{1}H-NMR(DMSO-d_6, 300 MHz, 100°C):δ= 1.20 (t, *J*=7.2 Hz, 3H), 1.39 (d, *J*=6.4 Hz, 3H), 1.45 (s, 3H), 1.48-1.62 (m, 1H), 1.82-1.92 (m, 1H), 2.02-2.13 (m, 1H), 2.29-2.38 (m, 1H), 3.63-3.72 (m, 1H), 4,15 (dq, J_1=0.2 Hz, J_2=7.2Hz, 2H); ^{13}C-NMR (DMSO-d_6, 75 MHz, 100°C):δ=13.23 (q), 14.83 (q), 18.13 (q), 25.60 (t), 30.61 (t), singlet missing: under DMSO resonance, 61.00 (t), 62.58 (d), 132.2 (s). **9** *Trans* isomer: ^{1}H-NMR(DMSO-d_6, 300 MHz, 100°C):δ= 1.20 (t, *J*=7.2 Hz, 3H), 1.36 (d, J= 6.6Hz, 3H), 1.61 (s, 3 H), 1.54-1.63 (m, 1H), 1.85-2.39 (m, 3H), 3.82 (m, 1H), 4.24 (q, *J*= 7.2 Hz, 2H); ^{13}C-NMR (DMSO-d_6, 75 MHz, 100°C):δ= 16.65 (q), 19.78 (q), 21.20 (q), 29.65 (t), 35.60 (t), singlet missing: under DMSO resonance, 54.38 (d), 71.73 (t); 170.34 (s); MS=188[M^++1].